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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/883,550	06/18/2001	William E. Marshall	P01936US5	1897

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801 GRAND AVENUE
SUITE 3200
DES MOINES, IA 50309-2721

EXAMINER

ZEMAN, ROBERT A

ART UNIT	PAPER NUMBER
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1645

DATE MAILED: 03/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/883,550	MARSHALL, WILLIAM E.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 January 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,4-8 and 10-19 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,4-8 and 10-19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 1-20-2004 has been entered.

The amendment filed on 1-20-2004 is acknowledged. Claims 1, 12 and 17 have been amended. Claims 2-3 have been canceled. Claims 1, 4-8 and 10-19 are pending and currently under examination.

Declaration

The declaration by William E. Marshall filed under 37 CFR 1.132 is acknowledged and has been fully considered.

Claim Rejections Withdrawn

The rejection of claim 12 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "stress response factors (SRFs) <10kDa" is withdrawn in light of the amendment thereto.

Claim Rejections Maintained and New Grounds of Rejection

35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-8 and 10-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 17-19 are rejected under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase “sequential periods of stress” for the reasons set forth previously in the rejection of claims 17-19.

Applicant argues:

1. Amended claim 17 further defining the phrase “sequential periods of stress” thereby making them definite.

Applicant’s arguments have been fully considered and deemed non-persuasive. Contrary to Applicant’s assertion, the amendment to claim 17 is insufficient to overcome the rejection. While Applicant has defined what constitutes a “period”, it is still unclear whether the stress factor changes with each successive “period”, whether there are rest periods (i.e. removal of stress factors) in between these “periods”? If not, what demarcates the end of one period and the onset of the next? Additionally, claim 18 recites the transferring bacteria to a non-nutritive media

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and the subsequently transferring the bacteria to non-nutritive media. It is unclear whether this is considered a single "stress period" or multiple periods.

Claims 4-5 are vague and indefinite as they are dependent on a canceled claim.

Claim 1 is rendered vague and indefinite by the use of the phrase "activating and modulating". It is unclear what is meant by "modulating" and why "activation" is not considered a type of "modulation.

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The rejection of claims 1, 4-8 and 10-19 under 35 U.S.C. 103(a) as being unpatentable over De Vuyst et al. (Microbiology, Vol. 142, 1996, pages 817-827) is maintained for reasons of record. The cancellation of claims 2-3 has rendered the rejection of these claims moot.

Applicant argues:

1. Examiner is misinterpreting Applicant's invention that is not related to bacteriocins.
2. The declaration by Dr. Marshall clearly establishes that the SRF compositions of the invention do not include bacteriocins or other compositions with bactericidal properties.

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3. The results of Figure 1 demonstrate that the preparations of the invention obtained from *L. monocytogenes*, *L. plantarum* and *E. faecium* do not inhibit the growth of *Lactobacillus helveticus*.
4. The bacteriocin Nisin does inhibit the growth of *Lactobacillus helveticus*.
5. Figure 2 shows that stressing *L. monocytogenes* or even twice stressing *L. plantarum* and *E. faecium* or stressing heat killed *L. plantarum* and *E. faecium* do not result in bactericidal activity against *L. helveticus*.
6. Figure 3 demonstrates that no bacteriocins against *L. helveticus* are produced by stressing, *L. caseii*, *L. plantarum* or *E. faecium*.
7. Figure 4 shows that the bacteriocin Nisin inhibited 7 strains of bacteria while the SRFs collected from the same strains and *L. caseii* did not inhibit growth.

As outlined previously, De Vuyst et al. disclose methods of producing low molecular weight proteins from bacteria by subjecting them to a number of stresses. By definition, these proteins are stress response factors. These stresses include: a change in temperature, a change in pH, a change in biomass (crowding or decreasing the amount of media), and adding toxins such as ethanol (see abstract). Subjecting the lactic acid bacteria to any of these stressors results in the release of low molecular weight monomers of bacteriocin (approx 6 kDa or less) that oligomerize to be about 30 kDa. De Vuyst et al. remove components larger than the bacteriocin monomer (see page 818, column 1). De Vuyst et al. further disclose that these bacteriocins are able to kill or harm other bacterial species and suggest the use of said bacteriocins as food additives (see page 818, column 1). Consequently, it would have been obvious to one of ordinary

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skill in the art at the time the invention was made to have followed the suggestion of De Vuyst et al. and administer the low molecular weight proteins produced by stressed bacteria to animals since said proteins (bacteriocins) can act to kill or render harmless other strains of bacteria and thereby enhancing the ability of an animal's immune system to deal with bacterial infections minimizing the complications associated with introducing a bacterial strain into the normal flora of an animal. Moreover, the internalization of said proteins by an animal would stimulate its the immune system.

Moreover, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the SFR do not have bactericidal properties) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The instant claims are drawn to **all** factors produced with a molecular weight less than 10 kDa in response to nutrient deprivation.

The rejection of claims 1, 4-8, 10-15 and 17-19 under 35 U.S.C. 103(a) as being unpatentable over De Vuyst et al., cited above, in view of Nanji (U.S. Patent 5,413,785 – IDS-2) is maintained for reasons of record. The cancellation of claim 9 has rendered the rejection of this claim moot.

Applicant argues:

1. There is no suggestion of the claimed invention or the expectation of success in combining the cited references.

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2. The cited **reference** does not teach or suggest every element of the claimed invention that must be identically disclosed, in a single reference.
3. It is required that both the suggestion and the expectation of success must be found in prior art. This is not accomplished in regard to De Vuyst et al.
4. SRFs do not directly kill bacteria, as do bacteriocins.
5. Nanji does not reference applicant's SRF that are present in all stressed bacteria.
6. Nanji teaches away from the concept that ordinary lactobacilli that do not inhibit E. coli could, when stressed, provide protection against LPS.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Points 1 and 3, De Vuyst et al. disclose methods for producing low molecular weight proteins from stressed bacteria (bacteriocins) and suggests adding said proteins to food (see above). Nanji discloses the administration of lactic acid bacteria to humans, livestock and other animals for protection against endotoxin-mediated shock. Nanji further discloses that said bacteria should be able to produce anti-microbial substances and/or produce proteinaceous antagonistic substances (bacteriocins) since said substances aid in preventing the growth of gram-positive and gram-negative bacteria in the intestine and thereby reducing endotoxin formation (see column 10, lines 40-45). Reduction of endotoxin levels, in turn, reduces the effects of said endotoxin on the immune processes of the animal. Therefore, it would have been obvious to one of ordinary skill in the art to use the bacteriocins disclosed by De Vuyst et al. in the treatment methodologies of Nanji in order to take advantage of the immune enhancing effects of the bacteriocins while minimizing the complications associated with introducing a bacterial strain into the normal flora of an animal. One would have had a high

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expectation of success since De Vuyst et al. disclose the use of said bacteriocins as a food additive and Nunji disclose the importance of bacteriocins in reducing endotoxin levels and thereby reducing the deleterious effects of said endotoxin on the animal's immune system.

Moreover, in response to applicant's argument that the references fail to show certain features of applicant's invention (Points 4 and 6), it is noted that the features upon which applicant relies (i.e., the SFR do not have bactericidal properties) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The instant claims are drawn to **all** factors produced in response to nutrient deprivation.

With regard to Point 5, the instant claims are not drawn to SRFs that are produce by all stressed bacteria. The instant claims are drawn to **any** factor (protein) with a molecular weight less than 10kDa produced in response to nutrient deprivation.

The rejection of claim 16 under 35 U.S.C. 103(a) as being unpatentable over De Vuyst et al., cited above, in view of Perdigon et al. (Journal of Food Protection Vol. 53, No. 5, pages 404-410, 1996 – IDS-2) is maintained for reasons of record.

Applicant argues:

1. Perdigon teaches that the health benefits of feeding milk fermented with lactobacilli is due to the interaction between the bacteria and the milk solids and that these effects are limited to and based upon the presence of milk.
2. Perdigon teaches away from the use of stressed bacteria alone.

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3. The Examiner is using hindsight application of the Applicant's specification.

Applicant's arguments have been fully considered and deemed non-persuasive.

Claim 16 is being examined as a method of modulating the immune system of an animal by administering low molecular weight stress proteins as an adjuvant.

The teachings of De Vuyst et al. are discussed above. Perdigon et al. disclose the use of lactic acid bacteria and the proteins produced therein as immunogens and adjuvants in the generation of protection from enteropathogens (see abstract, page 404, column 2 and pages 408-409). It would have been obvious to one of ordinary skill in the art at the time the invention was made to **use the low molecular weight proteins disclosed by De Vuyst et al. as adjuvants** for the induction of a immune response to another co-administered pathogen since Perdigon et al. discusses the use of lactic acid bacteria (and the proteins produced by said bacteria) as adjuvants for enteropathogens (an increased immune response to said enteropathogens was also disclosed) and De Vuyst et al. disclose that proteins produced by lactic acid bacteria have an immunomodulatory effect. Consequently, since the lactic acid bacteria serve as the immunogen, they do not need to be separated from the milk in order to meet the limitations of the rejected claim.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the

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applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert A. Zeman
March 23, 2004


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